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ASSIGNING VALUES TO NONDETECTED/NONQUANTIFIED PESTICIDE RESIDUES IN HUMAN HEALTH DIETARY EXPOSURE ASSESSMENTS (11/30/98 DRAFT)

Executive Summary

Residue data are used by the Agency to support the establishment or reassessment of a pesticide tolerance associated with a particular food use. In some cases, a portion of the measurements of the levels of pesticide residue present on food shows no detection of residues. These "nondetects" (NDs) do not necessarily mean that the pesticide is not present at any level, but simply that any amount of pesticide present was below the level that could be detected or reliably quantified using a particular analytical method.

The primary science policy issue concerning NDs is what value EPA should assign to them when estimating dietary exposure and risk from a pesticide. The reason this is an important issue stems from the new requirements that the Food Quality Protection Act of 1996 (FQPA) imposes on EPA. Among other things, FQPA established a stringent health-based standard ("a reasonable certainty of no harm") for pesticide residues in foods to assure protection of the public health, including sensitive populations such as infants and children, from unacceptable pesticide exposure and risks. The general issue is how to make EPA's exposure and risk assessments as accurate and realistic as possible. The specific issue addressed in this paper is what values should the Agency assign to residue samples which show no detected levels of a pesticide such that the exposure estimates are reasonable, accurate and realistic?

This science policy paper describes the value that EPA will assign to NDs under different circumstances when EPA conducts a dietary exposure and risk estimate for a pesticide food use. In summary, EPA will assign a value of zero to the proportion of the data set corresponding to the percentage of the commodities known **not** to be treated with the pesticide. For the remainder of the data points for pesticide-treated commodities, EPA will use the following assumptions: (1) if a valid Limit of Detection (LOD) exists, EPA will use ½ LOD as the assigned value for NDs when conducting dietary exposure and risk assessments; (2) if an LOD is not available, but a valid Limit of Quantitation (LOQ) exists, EPA will use ½ LOQ for the NDs; (3) if neither an LOD nor an LOQ is available, EPA will use the Lower Limit of Method Validation (LLMV) for the NDs; and (4) if nonquantifiable residues are detected between the LOQ and LOD, EPA will use ½ LOQ for those NDs.

In adopting this science policy, EPA's goal is to avoid underestimating exposure to potentially sensitive or highly exposed groups such as infants and children while attempting to approximate actual residue levels as closely as possible. Both biological information and empirical residue measurements support EPA's belief that this science policy is consistent with these goals. Recognizing, however, that these assumptions may, in some cases, either overestimate or underestimate exposure, EPA's policy will be to perform a "sensitivity analysis" to determine the

impact of using different assumptions, e.g., assuming NDs = LOQ or NDs = zero, on the Agency's assessment of risk for the pesticide under evaluation.

This paper also refers to two related papers being made available for comment at the same time that address other aspects of the primary science policy issue mentioned above: (1) "A Statistical Method for Incorporating Nondetected Pesticide Residues into Human Health Dietary Exposure Assessments" and (2) "Proposed Threshold of Regulation Policy When a Food Use Does Not Require a Tolerance."[1]

I. INTRODUCTION

A. Scope

This science policy paper applies only to dietary exposure via the food supply and, more specifically, only to the refinement of dietary exposure by calculation of Anticipated Residues (ARs), a risk assessment refinement tool. This paper does not apply to the determination of an appropriate pesticide tolerance which is an enforcement tool. Although calculating ARs (typically the average or a given percentile of a data set) is just one aspect of the refinement of dietary exposure estimates, it involves many integrally-related considerations. One such consideration is the treatment of data points at or below the Limit of Quantitation (LOQ) and those below the Limit of Detection (LOD) (see definitions in Section II.A.).

B. How EPA Performs Exposure Assessments for Pesticides in Food

1. Starting with worst case (tolerance) levels. Pesticide dietary risk assessments are initially conducted using conservative assumptions such as tolerance-level residues in crops, maximum theoretical livestock diets, highest field trial residue values, and 100% of the crop being treated. If there is a reasonable expectation of residues resulting from a given pesticidal food use but any residues that may occur are nondetectable, the Agency has historically established the tolerance for that pesticide in that food at the LOQ; the Agency continues to support that regulatory approach.

2. Refining estimates using actual/anticipated residues. Worst-case assessments described above may result in an **apparently** unacceptable acute and/or chronic dietary risk. In such cases, resources necessary to refine dietary exposure assessments to derive more realistic estimates are often warranted. To further refine dietary exposure, calculations may include percent-crop-treated data, more realistic livestock diets, averages of field trial data or a certain percentile of

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monitoring data, reduction of residues upon cooking or processing, and, in some cases, probabilistic analyses of composited or even single serving-size samples. The refined exposure estimates, or ARs, are so designated because they are more likely to approximate the pesticide residues we anticipate humans will actually consume in their diets. The ways in which the data are refined depends on such considerations as what data are available, the relative confidence the Agency has in these data, the residues of toxicological significance and which of these are detected by the analytical method(s) used, the metabolic profile over time, and whether the exposure duration/toxicological endpoints dictate the conduct of an exposure assessment for use in an acute or a chronic dietary risk assessment, or both.

3. Many samples do not have quantifiable/detectable residues. Often, a residue chemistry data set for a given crop/chemical/data source combination of potential use in exposure refinement contains some samples that are reported as not bearing detectable or quantifiable residues, i.e., residues are less than the LOD or LOQ. This is frequently the case for early season applications, long treatment-to-harvest intervals, and/or monitoring of the food supply closer to the point of consumption. The principal focus of this paper is to detail what numerical value should be assigned to each sample reported as being <LOD or <LOQ for use in a quantitative exposure assessment.

C. Past Science Policy Positions

In the past, EPA has issued two policy documents that provide somewhat different recommendations regarding the assumptions EPA would make to determine the level of pesticide residue present in samples reported as NDs when performing dietary exposure assessments. The 6/13/96 "Policy for Performing Acute Dietary Exposure Assessments" states that when averaging residues in blended commodities the LOD should be used if residues are nondetectable and the LOQ should be used if residues are detectable, but not reliably quantified. The rationale for using the full LOD or LOQ for blended foods in the acute dietary exposure assessment policy was that these reflect analytical capability/confidence and would represent the upper end of the exposure distribution, which was considered appropriate for acute assessments. The 1/15/98 Draft policy re. Anticipated Residues for Chronic Dietary Exposure Assessments states that ½ LOQ should be used for NDs. The rationale for use of ½ LOQ in the draft chronic dietary exposure assessment guidance was that, in the absence of data, ½ LOQ was considered an arbitrary, yet reasonable, estimate of an average residue below the level of quantitation; average residue values were considered appropriate ARs for chronic assessments.

In comparing these two policies, EPA recognized that the public could find it confusing and arguably inconsistent to estimate the residue value associated with the very same ND sample as ½ LOD or ½ LOQ in a chronic assessment and also as the full LOD or the full LOQ in an acute assessment. For example, if the LOD or LOQ were 0.1 ppm, how could EPA conclude that the same sample, in which no residue was measured, contains both 0.05 ppm *and* 0.1 ppm of a given residue? In light of this kind of question, EPA decided to reexamine its science policy regarding NDs to assure a scientifically supportable basis for assigning residue values. Clarification of this

issue is particularly critical in light of the aggregate and cumulative risk assessments now required under the Food Quality Protection Act (FQPA). In order to provide guidance concerning the assignment of values to NDs in the calculation of ARs, this science policy paper addresses the following question:

- **Under what circumstances, during the conduct of a dietary exposure assessment, is it appropriate to use "true zero", ½ LOD, LOD, ½ LOQ, LOQ, or some other value to represent the magnitude of the residue in field trial and monitoring samples reported as "nondetected" or "nonquantified"?**

II. POLICY FOR ASSIGNING NUMERICAL VALUES TO SAMPLES REPORTED AS NONDETECTED OR NONQUANTIFIED

A. Definitions

Confusion has arisen over the years due to definitional differences between LOD and LOQ, a lack of distinction between the two, preference for one over the other, the proliferation of several synonymous terms such as "limit of determination" or "limit of sensitivity," and the fact that there are situations in which one is, indeed, more appropriate than the other. In many cases, a sample is reported to contain nondetectable residues when, upon further investigation, the proper designation should have been "nonquantifiable," or vice versa.

1. Limit of detection (LOD). LOD can be defined as the lowest concentration that can be determined to be statistically different from a blank (negative control sample). This concentration is often recommended to be three standard deviations above the measured average difference between the sample and blank signals. In practice, detection of an analyte by an instrument is often based on the extent to which the analyte signal exceeds peak-to-peak noise (Keith et al., 1983). Samples that do not bear residues at or above the LOD are often referred to as "non-detects" (NDs). EPA is developing new guidance that will outline procedures to properly determine LOD experimentally and statistically.

2. Limit of Quantitation (LOQ). LOQ can be defined as the level above which quantitative results may be obtained with a specified degree of confidence. The corresponding sample/blank difference is often given as 10 standard deviations at the 99% confidence level (Keith et al., 1983). LOQ is typically used to define the lower limit of the useful range of the measurement technology in use. Samples that do not bear residues at or above the LOQ are often referred to as "nonquantifiable." Again, the Agency is preparing new guidance that will soon be available to permit experimental and statistical determination of LOQ.

3. Lower limit of method validation (LLMV). There are cases in which a laboratory does not stringently determine the LOD and LOQ of a particular substrate/method/equipment combination but, rather, a "Lower Limit of Method Validation" (LLMV) is determined that could be higher than the true LOQ within the capability of the method. The LLMV is simply the lowest

concentration at which the method was validated. In these cases, neither the method limit of first choice (LOD) nor second choice (LOQ) was demonstrated and the Agency would request that an LOQ be estimated by the registrant or interested party from the LLMV, chromatograms and other available information.

B. Policy on Use of Percent of Crop Treated

The Agency continues to support the use of "true zero" for that number of samples directly proportional to the percent of crop not treated, provided that percentage (or greater) of samples have been reported as "nondetects" in the case of those crops for which monitoring data are chosen as the basis for ARs. This has often been done in recent years to generate average exposure values for use in chronic/cancer risk assessments and for blended commodities for use in acute risk assessments. Whether the maximum, average, or some other percent-crop-treated figure would be used should be decided on a case-by-case basis considering such factors as whether the percent of crop treated fluctuates from year to year or whether there is an increasing or decreasing trend.

The Agency must determine which "nondetect" samples should be represented by zero in a ratio directly proportional to the percent of crop not treated. A range of interlaboratory LOD variation of ≥35x has been observed for a single chemical/crop combination in one residue monitoring data set. In calculating average residues when a variety of limits of detection exist, the average residue value calculated should incorporate a **weighted** average of the LODs **from treated commodities in which no residues were detected**. Such a calculation should not incorporate one-half of the overall average LOD from all laboratories. For example, if 80% of a crop is not treated, but 90% of the monitoring samples in a data set is reported as <LOD, then 80% of the samples (using a weighted average of the LODs of the various samples, if more than one LOD is reported) would be assigned a value of zero, 10% would be designated as ½ LOD, and 10% of the samples bear the reported quantifiable residues.

C. Basis for Using ½ LOD or ½ LOQ in Calculating Anticipated Residues

Frequently, data sets used in calculating anticipated residues for use in risk assessment contain at least some measurements for which the chemical analyst reported residue concentrations at levels "below the limits of detection or quantitation." The fact that no residues are detected does not necessarily mean none are there. Residues may exist at levels that are too low to detect. If the Agency has information demonstrating that a crop sample *was* treated with the pesticide in question, but residues were *not* analytically detected, there are a number of options available for dealing with these nondetectable values and integrating this information into pesticide dietary exposure assessments. The two extreme options would be 1) assume that if residues were not detected, that they are not present (i.e., residues concentrations are zero); or 2) assume that if residues were not detected (at some limit of detection), that they are present at *just* below that limit of detection. The former option would lead to the least conservative (i.e., least health protective) exposure estimate since the Agency would be assuming nondetectable residues were

actually zero; the latter option would result in the most conservative (i.e., most health protective) estimate since the Agency would be assuming that nondetectable residues were actually present at *just* below the analytical limit of detection.

EPA believes that neither approach reasonably represents reality, particularly in data sets in which many nondetects are present. Rather, biological information and empirical residue measurements indicate that residue data sets (including the NDs) are normally (or lognormally) distributed. On a theoretical basis, concentrations of pesticides in food crops might be expected to be a Random-Product process and the Theory of Successive Random Dilutions (SRD) would predict that concentrations of pesticides would be lognormal (Ott, 1995). In addition, a fair amount of empirical evidence for a lognormal distribution of pesticides in foods exists from a recent study by the UK's Ministry of Agriculture, Fisheries, and Food (MAFF) in which thousands of individual serving sized samples were analyzed for a variety of pesticides and found to follow in most cases a lognormal distribution (MAFF, 1997).

Given the above information, the Agency has chosen to assign a residue value of ½ LOD (or ½ LOQ if an LOD has not been determined) to samples with no detectable residues <u>if it is known or believed that these samples have been treated with a pesticide</u>. This is believed to represent a minimal distortion of reality if only a small proportion (e.g., less than approximately 10-15%) of the data are below detectable limits. The use of ½ LOD or ½ LOQ for nondetectable samples is widely used in the risk assessment community and is advocated by EPA (EPA, 1996) when the appropriate conditions are met.

D. Policy When an LOD Has Been Properly Determined

The selection of a numerical value to represent NDs in a refined dietary exposure assessment depends on the level of confidence the Agency has in the supporting documentation of the various method limits under consideration. For the Agency to have a high level of confidence, the claimed LOD must be demonstrated using chromatograms, calculations and statistics as noted above; guidance concerning determination of LOD and LOQ will be provided in a separate document. In accordance with OPPTS Test Guidelines - Residue Chemistry 860.1340(c)(2)(iii), the procedures used by a laboratory to determine the LOD and LOQ should be fully explained and/or copies of any appropriate publications should be submitted with the analytical method description to the Agency.

In the case of anticipated residue calculations for either acute or chronic risk assessments, if appropriate, it is preferable to extrapolate from those values in the data base which are greater than the LOQ to estimate levels in those samples below the LOQ or LOD. Proposed guidance for performing such imputations is currently available for public comment in the document entitled "A Statistical Method for Incorporating Nondetected Residues into Human Health Dietary Exposure

Assessments."[2] In those cases where it is not possible or chosen to impute values below the LOQ, the LOD is preferred to represent NDs, provided that the LOD has been properly determined, and provided that sample chromatograms and other information support such an assignment. The actual numerical value to be entered into the AR calculation or used to populate the electronic residue data file (RDF) is **½ LOD**. Particularly in those cases in which acute dietary risk is only marginally acceptable and ½ LOD is used for a significant portion of the samples, this situation should be emphasized in the risk characterization and the initiation of a sensitivity analysis (see II.H. below) should be considered.

E. Policy When an LOQ Has Been Properly Determined

If it is decided that imputations below the LOQ are not practical or appropriate and if an LOD has not been properly determined (see II.D. above), the LOQ is chosen to numerically represent NDs in a data set. In other words, Agency scientists must determine whether an LOQ has been experimentally and statistically demonstrated and if a given sample may be accurately represented by ½ LOQ as demonstrated by chromatograms and other information. The actual numerical value to be entered into the AR calculation or to populate the electronic residue data file (RDF) is **½ LOQ**.

The issue arises regarding how to deal with detectable, yet nonquantifiable residues, i.e., residues falling between the LOD and the LOQ. The 6/13/96 acute dietary exposure assessment policy stated that such residues would be estimated to be at the LOQ. However, data indicate that use of the full LOQ will consistently overestimate exposure regardless of whether acute or chronic risk is being assessed. Therefore, such samples should typically be represented numerically in the refined exposure assessment/RDF files as **½ LOQ** when assessing both acute and chronic risk. If information is available indicating that most residue values are estimated to be just below the LOQ, a decision will be made on a case-by-case basis regarding the appropriate value to assign to NDs. This science policy is consistent with the extensively peer reviewed OPPTS Test Guidelines Series 875 - Occupational and Residential Exposure which state that ½ LOQ should be used to represent samples bearing detectable residues ≤LOQ. The rationale for selection of this limit, which could vary by commodity, method or data set/source, should be explained clearly in the risk characterization. If available and clearly supported by raw data (chromatograms, etc.), the analyst's estimate of the residue between the LOD and the LOQ may, at the discretion of the Agency, be used as a means of further refinement of the dietary exposure. If a significant portion of the residue values was derived via the analyst's estimation of values between the LOD and LOQ, this must be noted in the risk characterization.

F. Policy When Neither an LOD Nor LOQ Has Been Properly Determined

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If neither the LOD nor the LOQ has been properly determined, the full LLMV (lowest concentration at which the method was validated) will be used in risk assessment. The rationale for this policy is that the Agency has less confidence in data samples when an LOD or LOQ cannot be determined or estimated. Accordingly, to assure that actual dietary exposure will not be underestimated using such data, the Agency will use the full LLMV for each ND of a treated sample in this situation. However, if the registrant or some other party is capable of accurately estimating an LOQ using chromatograms and other relevant information, EPA will allow the use of a full LOQ estimated from the LLMV. The rationale for selection of this limit, which could vary by commodity, method, or data set/source, would be explained clearly in the risk characterization. EPA believes that the assignment of the estimated LOQ as the value for NDs would not underestimate dietary exposure in this situation.

G. Considerations Related to Pesticides Having Multiple Metabolites of Concern

A value of zero may also be appropriate to represent "nondetects" for one or more **analytes of concern** provided this decision is supported by such information as metabolism studies, data at shorter preharvest intervals (PHIs), exaggerated rate data, etc. This approach may be appropriate only for certain crops or certain use patterns. On a case-by-case basis, plant or livestock metabolism data, data reflecting exaggerated application rates and/or short PHIs, close examination of the chromatograms, consideration of the analytes determined by the analytical method(s), and other information may be used singly or in conjunction to formulate a weight-of-the-evidence argument in favor of (or against) use of true zero to represent the level of one or more analytes of toxicological concern potentially present in samples denoted as bearing less than LOD/LOQ residues. This procedure could be particularly important for pesticides having several residues of toxicological concern whereby, using the above information, the chemist gains confidence that only a subset of the terminal residues will be present at normal harvest time; zeros could be used for the other analytes of concern. On an international level, a similar approach is used by the Food and Agriculture Organization/World Health Organization's Joint Meeting on Pesticide Residues in the case of pesticides having a chronic toxicological endpoint.

Note that the LOD and/or LOQ is often not established for all residues of toxicological significance if the method is capable of determining the residues at all. This is particularly the case with multiresidue monitoring methods. For example, FDA often reports only residues of the parent compound. USDA's Pesticide Data Program (PDP) often attempts to analyze all residues of toxicological significance; however, there are certain metabolites of concern that are not sought by PDP due to analytical difficulty or due to the unavailability or expense of analytical standards. As a result, difficulty arises when attempting to sum the residues of multiple analytes of concern because a numerical limit is not available to assign to nondetectable levels of one or more of the residues of concern. Such shortcomings may render one or both sources of monitoring data of limited value to the refinement of dietary exposure estimates unless metabolism studies and other information can be used to establish a ratio between the concentration of one or more analyte(s) to the concentration of toxicologically significant residues not determined by the method. Decisions on how to use such residue data will be made on a case-by-case basis.

H. Performance of a Sensitivity Analysis

In general, assigning numerical values to NDs as described above is not expected to significantly affect the Agency's risk estimate or alter the risk management decision. However, the Agency, under certain circumstances, will perform a sensitivity analysis if it is believed that the substitution of ½ LOD or ½ LOQ values for nondetects has significantly affected the outcome of a risk assessment and/or the Agency's risk decision. That is, if the Agency risk assessment shows *unacceptable* risks when ½ LOD values are used for nondetects, EPA will attempt to demonstrate that the use of ½ LOD has not *by itself* controlled the risk decision by *re-estimating* risks with true zero substituted for ½ LOD or ½ LOQ. Conversely, if the risk assessment shows *acceptable* risk when ½ LOD values are substituted for nondetects, we will re-estimate the risks with the full LOD or LOQ substituted for ½ the LOD or LOQ. If the Agency risk assessment changes as a result of assigning these alternate values, the sensitivity analysis will have demonstrated that the Agency risk assessment is sensitive to assumed concentrations for the nondetects. EPA may then request that additional data and/or an improved analytical method be developed and submitted.

III. RELATIONSHIP TO OTHER OPP POLICIES

A. Determining the Tolerance When All Data Points are Reported as Nondetectable

Fairly often, EPA establishes a tolerance for pesticide residues in/on a commodity because Agency scientists conclude that even though there is a reasonable expectation of finite residues occurring in that commodity as a result of the proposed/registered use pattern, all samples of the commodity were reported to contain residues below the LOD or LOQ. This situation often occurs if the application rate is very low, the pesticide is used early in the crop season, or if the treatment-to-harvest interval is long. In such cases, EPA may have information from metabolism/laboratory studies or exaggerated application rate studies to indicate that finite, albeit nondetectable, residues are expected to occur in the field at the pesticide label rate. In these circumstances, tolerances are established at the LOQ of the analytical method for the commodity in question. In the case of livestock, this is in accordance with 40 CFR 180.6(a)(2); there is no corresponding regulation for plant commodities although the same concepts are applied.

B. Determining the Necessity of a Tolerance When There is no Reasonable Likelihood of Finite Residues

Occasionally, particularly in the case of livestock commodities, residues are not reasonably expected to occur in a commodity given such information as the use pattern, chemistry of the compound, and/or metabolism of the compound. This determination is typically based upon metabolism studies and/or exaggerated rate studies. In these cases, a tolerance is typically determined not to be necessary and no exposure is assumed in a dietary risk assessment. In the case of livestock, this is in accordance with 40 CFR 180.6(a)(3). Again, there is no corresponding regulation that applies to plants, but the same concepts are applied. Such determinations are rare in the case of plant commodities, but have been made in the case of seed

treatments, nonbearing tree crop treatments, and preplant soil treatment. A separate issue paper entitled "Proposed Threshold of Regulation Policy Defining When a Food Does Not Require a Tolerance" considers extending this basic approach to additional food uses if certain criteria are met (i.e., that exposure or risk from a food use is "essentially zero.") [3]

C. Procedures for Estimating Distribution of Residues in a Data Set Containing Treated Samples that are Below the LOD and/or LOQ

There may be instances in which a significant portion (e.g., more than 15%) of the residue data set contains non-detectable residues, when a sensitivity analysis reveals an inordinate effect of the ½ LOD or ½ LOQ assumption on the risk decision, or when it is simply decided that a more accurate assessment of residue levels is appropriate. In such circumstances, a separate policy describes the methodology for estimating residues below the LOQ using probabilistic methodologies. In general, the data should be normally (or log-normally) distributed, no more than 50% of the data set may be <LOD or <LOQ, and there may be only one LOD/LOQ level attributed to the database. Separate draft guidance already mentioned above (see footnote 1) is available for public comment on this topic.

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[3] This draft science issue paper is being made available for public comment for 60 days via an announcement in the Federal Register. EPA is seeking public comment on a series of draft documents concerning nine science policy issues in order to make the development of its FQPA-related science policies transparent and participatory for all interested parties.